Studies of the "Antihistaminic" Effect of Pyribenzamine Administered by Various Routes

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SUMMARY

Utilizing histamine electrophoresis, the degree and duration of "antihistaminic" effect of varying doses of Pyribenzamine® administered by different routes were studied.

Delayed action Pyribenzamine in 50 mg. and 100 mg. dosage exerted a small but measurable anti-wheaIing effect five hours after ingestion. The larger dose exerted approximately twice the effect of the smaller. The anti-wheaIing activity lasted five to six hours.

Pyribenzamine given intravenously affected the wheaIing response one hour after administration. A peak of activity was reached two to two and a half hours after injection, and "antihistaminic" effect continued for a total of five hours.

The inunction of 250 mg. and 500 mg. of Pyribenzamine in an ointment base resulted in sufficient absorption of the drug to produce a measurable anti-wheaIing effect. The "antihistaminic" activity was noted three hours after application and lasted 10 to 12 hours from the time of inunction.

SINCE the introduction of the first "antihistaminic" compound by Fourneau and Bovet in 1933 an almost limitless number of related and similarly acting compounds have become available. A variety of methods of administration, including oral, intravenous, inhalation, and topical routes, have been used. Despite the widespread use of these drugs and their administration by various methods, little is known about the exact manner in which they function in man. The time interval between administration and therapeutic effect, the duration of activity, the degree of "antihistaminic" action in relation to dosage, and the influence of method of administration, have not been completely studied in human beings. To obtain further data concerning these factors, the present study was undertaken.

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MATERIALS AND METHODS

Pyribenzamine® was administered to groups of ten subjects each in varying dosage by several routes. The "antihistaminic" effect in each instance was measured by histamine electrophoresis, a method described in detail by Cohen and Friedman.[1] Sternberg, Perry and LeVan[3] used this technique with modifications to determine the comparative "antihistaminic" activity of 13 commercially available "antihistaminic" drugs administered orally. Briefly, the method utilizes a 2-milliampere current for two minutes to introduce serial dilutions of histamine base into the skin of the flexor surface of the forearm. That dilution which produces diffuse wheaIing at the site of the positive electrode is considered to be the initial threshold dilution. This is not an actual quantitative determination of the amount of histamine base entering the skin but represents the concentration of histamine base per cubic centimeter of solution necessary to produce a wheaIing reaction. The "antihistamine" to be tested is then given and wheaIing threshold determinations made at varying intervals depending upon the route of administration of the drug. "Antihistaminic" activity is manifested by a raising of the threshold—that is, a more concentrated solution is necessary to produce diffuse wheaIing. The difference in micrograms of histamine base per cubic centimeter of solution between the initial threshold concentration and the subsequent threshold concentrations represents the amount of histamine base "blocked" by the "antihistaminic" drug administered.

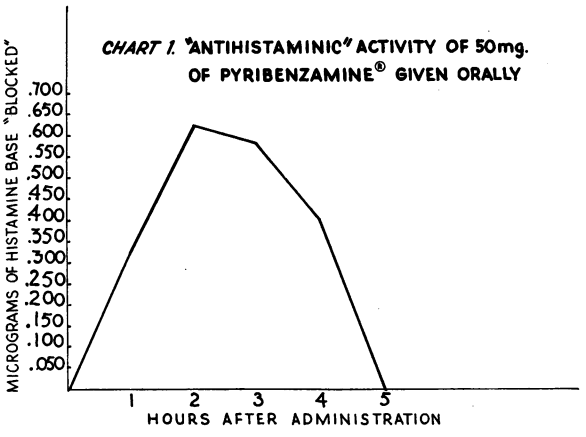
Using this method, Perry and Hearin[2] determined the degree and duration of the "antihistaminic" activity of 50 mg. of orally administered Pyribenzamine. The results of that study are shown in Chart 1.

It will be noted that the "antihistaminic" activity of Pyribenzamine orally administered reaches a maximum of 0.63 micrograms of histamine base "blocked" two hours after ingestion. This activity is maintained for another hour and decreases by the fourth hour; in five hours no effect can be measured.

RESULTS

Histamine electrophoresis, as described, was used to measure "antihistaminic" activity in the following studies:

1. Orally administered enteric coated (delayed-action) tablets of Pyribenzamine in 50 and 100 mg. doses were given to two groups of ten subjects each.



Whealing thresholds were determined at hourly intervals for periods ranging up to 12 hours.

2. Pyribenzamine was injected intravenously in 1 cc. and 2 cc. doses into 20 subjects, ten subjects receiving 25 mg. and ten subjects 50 mg. of the drug. Threshold determinations were done at half-hour intervals.

3. Cutaneous absorption of Pyribenzamine was studied by the inunction of 5 gm. and 10 gm. of a 5 per cent Pyribenzamine ointment* containing 250 mg. and 500 mg. of Pyribenzamine respectively. The ointment was applied to the inner aspects of the thighs of twenty subjects, ten in each group. Whealing thresholds were determined hourly up to 12 hours.

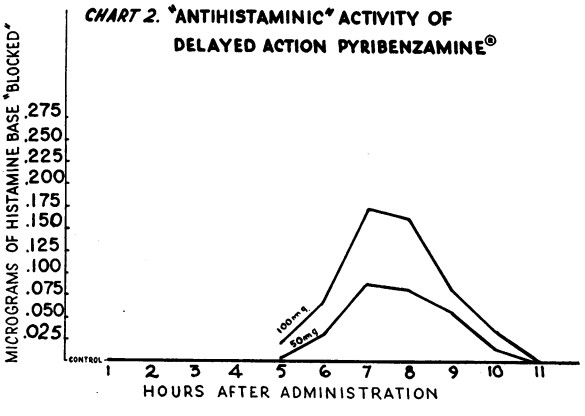
The difference between the initial and subsequent whealing threshold reactions, expressed in micrograms of histamine base per cubic centimeter of solution, were averaged for each of the groups studied. Placebo controls were given to groups of ten subjects each by the routes of administration used in this experiment. The subjects were males, white and negro, between 20 and 49 years of age. They received no oral medication for 24 hours before testing.

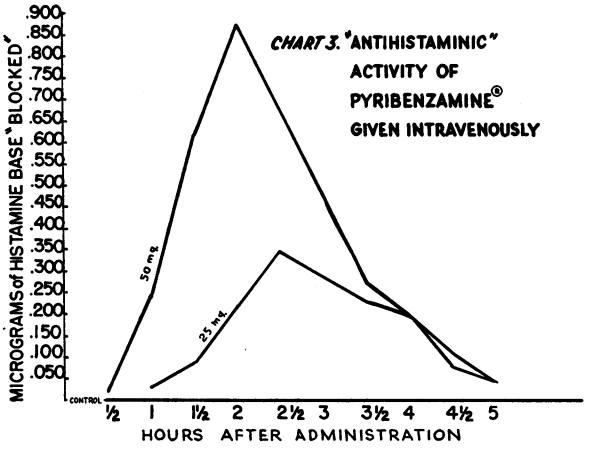
The results obtained by the oral administration of 50 and 100 mg. of delayed action Pyribenzamine are shown in Chart 2. A latent period of about five hours followed the ingestion of the drug. In six hours "antihistaminic" effect was manifested and reached a peak seven hours after the compound was taken. This maximum effect was 0.085 micrograms of histamine base "blocked" by administration of 50 mg. and 0.175 micrograms "blocked" by 100 mg. of delayed action Pyribenzamine. "Antihistaminic" activity was manifested up to ten hours after administration of the drug and for a period of five hours from the time its activity could first be measured by the method used. It will be noted in the chart that considerably more "antihistaminic" effect was obtained when a larger dose was given, but in both instances the form of the curve and the time relationships were identical. In control subjects receiving an oral placebo there was no change in the whealing threshold during a similar time period.

The "antihistaminic" effect obtained by the intravenous injection of 25 mg. and 50 mg. of Pyribenzamine is shown in Chart 3. A preparation of normal saline solution containing 25 mg. of Pyribenzamine per cubic centimeter was used. Thresholds were determined at one-half hour intervals. It will be noted that little measurable "antihistaminic" effect was present one-half hour after administration of 50 mg. of Pyribenzamine. The peaks of "antihistaminic" activity—0.88 and 0.35 micrograms of histamine base per cubic centimeter "blocked" by 50 mg. and 25 mg. of Pyribenzamine, respectively—were reached in two to two and a half hours. The 50 mg. dose resulted in considerably more "antihistaminic" activity than did the 25 mg. dose, although the duration of activity was the same, approximately five hours.

The ten control subjects, given 2 cc. of normal saline solution by injection, had no change in whealing threshold during a similar period.

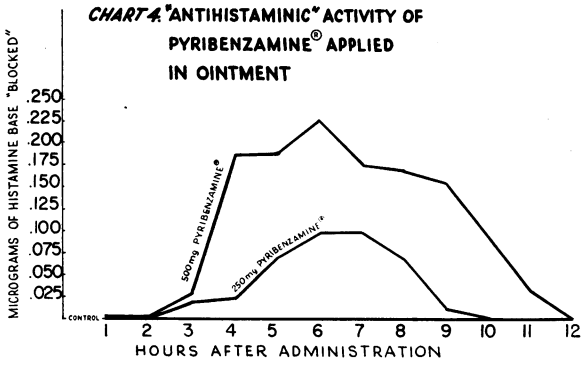
One group of ten subjects was given 250 mg. of Pyribenzamine in a 5 per cent ointment by inunction and another group of ten was given 500 mg. by the same route. The ointment was thoroughly rubbed





*The ointment base consisted of cholesterol, stearyl alcohol, lanolin anhydrous, white petrolatum and white wax.

into the inner aspect of the thighs for a five-minute period. Threshold determinations were done at hourly intervals. A latent period of about three hours was evident (Chart 4) followed by a measurable "antihistaminic" effect. The peaks of activity —0.100 and 0.225 micrograms of histamine per cubic centimeter "blocked" by 250 and 500 mg. of Pyribenzamine, respectively—were reached six hours from the time of inunction. "Antihistaminic" activity was measurable up until nine hours following the application of 250 mg. of Pyribenzamine and eleven hours after the application of 500 mg. Ten subjects treated with the ointment base alone had no change in the whealing thresholds.



DISCUSSION

The "antihistaminic" effect of 50 mg. and 100 mg. of "delayed action" Pyribenzamine tablets as measured by histamine electrophoresis is less than that of the more rapidly absorbed 50 mg. tablet. In a previous study the authors demonstrated a peak of "antihistaminic" activity—0.7 micrograms of histamine base "blocked"—two hours following the oral ingestion of the more rapidly acting 50 mg. tablet. As shown in Chart 2, delayed action Pyribenzamine in 50 mg. dosage exerted an "antihistaminic" effect of 0.085 micrograms of histamine base "blocked" while 100 mg. resulted in a "blocking" effect of 0.175 micrograms. The peak of "antihistaminic" activity of delayed action Pyribenzamine was reached seven hours after ingestion of the drug. Previous studies of the disintegration time of the enteric coated tablets used in this experiment indicate that the release of Pyribenzamine begins approximately five hours after ingestion. However, the coating has been designed to perforate slowly rather than to completely disintegrate within a short period of time. Hence only small amounts of Pyribenzamine are released at any given time. It appears likely that a greater degree of "antihistaminic" effect would be measurable if the enteric coating were to disintegrate rapidly after an initial four- to five-hour delay.

As shown in Chart 3, the intravenous administration of 50 mg. of Pyribenzamine resulted in a pronounced degree of "antihistaminic" activity. A peak of 0.88 micrograms was reached two hours after injection, as compared to a peak of 0.7 micrograms two hours after the oral administration of the 50 mg. rapidly acting tablet. Intravenous injection of 25 mg. resulted in a peak of activity of 0.345 micrograms of histamine base "blocked." A latent period of one-half hour to one hour followed the injection of the drug irrespective of dosage. This suggests the possibility that Pyribenzamine must first undergo a metabolic change before it causes antiwhealing activity. Further clarification of this phenomenon is desirable. The five-hour duration of activity observed with orally ingested Pyribenzamine was likewise present following intravenous administration.

All of the persons receiving intravenous Pyribenzamine noted subjective effects in varying degree. These included vertigo, drowsiness, a sense of relaxation, nausea, and consciousness of respiration. Subjective effects were noted with both 25 mg. and 50 mg. doses of Pyribenzamine and appeared shortly after administration of the drug. Rapid injection produced more pronounced symptoms than did slow introduction of the Pyribenzamine. The symptoms persisted for periods ranging between 45 minutes and four hours. One of the most frequently observed effects was the complete relaxation experienced by many of the subjects. Several subjects remarked upon a sense of well-being with complete loss of nervous tension. This effect, if obtained consistently, might prove desirable in clinical syndromes of allergic disease characterized by apprehension and nervous tension. There were no local reactions observed at the sites of injection.

As shown in Chart 4, the inunction of 10 gm. of an ointment containing 500 mg. of Pyribenzamine into the thighs of ten subjects produced a measurable anti-whealing effect three hours after application. A peak of "antihistaminic" activity expressed as 0.23 micrograms of base "blocked" was reached six hours after inunction. Anti-whealing effect was measurable up to eleven hours after the ointment was applied. A similar response of lesser degree was obtained with 250 mg. of Pyribenzamine in 5 gm. of ointment. A peak of "antihistaminic" activity —expressed as 0.1 micrograms of histamine base "blocked"—was likewise reached six hours after the application. Anti-whealing effect was measurable up to eight hours following inunction. Several subjects complained of drowsiness, but it was difficult to determine whether or not this was due to the Pyribenzamine. Acute dermatitis developed in one instance three hours after the application of 10 gm. of 5 per cent ointment. The subject in whom this occurred was withdrawn from the test group.

From the foregoing it is evident that significant amounts of Pyribenzamine are absorbed through the skin. The use of Pyribenzamine ointment over large areas of the body may be expected to produce drowsiness, vertigo, and other side effects of Pyribenzamine. Sternberg and Taylor,[4] among others, have demonstrated the ability of topically applied Pyribenzamine to filter out ultra violet radiation. However, use of the drug in a prophylactic sunburn

lotion or cream is deemed inadvisable because of the significant degree of cutaneous absorption as well as possible sensitization to the drug.

The authors wish to emphasize that the electrophoretic method of measuring "antihistaminic" effect utilizes the whealing reaction. It is believed that the amount of histamine necessary to produce whealing is greater than the minimal amount of histamine capable of producing other allergic phenomena. Hence, satisfactory therapeutic effects may be obtained at "antihistaminic" levels well below the peaks of activity demonstrated in this study. Further, other reported actions of "antihistaminic" drugs, such as anti-acetylcholine, sympathomimetic or sympatholytic effects not studied in this experiment, may play a therapeutic role in allergic syndromes.

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Discussion by MOLLEURUS COUPERUS, M.D., *Los Angeles*

I have enjoyed this paper very much. The authors have emphasized again the need for a dependable quantitative method by which we can measure the antihistaminic activity of various compounds. It is evident from the results of many workers that the experimental antihistaminic activity of the various drugs now available is not necessarily a dependable guide to the therapeutic value of such drugs in clinical medicine; those giving experimentally the best results may not rank that high when subjected to clinical evaluation. Even the degree of effectiveness in preventing whealing from histamine cannot be translated directly into a comparable effectiveness in the treatment of urticaria. In spite of this limitation, the methods at present available for the study of antihistaminic activity have been of inestimable value, and with continued work such as has been reported in this paper more reliable results will be obtained.

Doctors LeVan, Sternberg and Perry have employed iontophoresis to introduce histamine into the skin, which has also been used by a number of other workers with satisfaction. In evaluating the results reported in this paper, we must remember that the rate and degree of absorption from the gastrointestinal tract of the orally administered antihistaminic are subject to marked variation, and only a large series would give us reliable results when using this route. The inunction method would be subject to similar variation in transepidermal absorption. These variable factors might be avoided perhaps to a large degree by injecting the histamine and its antagonists simultaneously into the skin, using a sufficient number of control injections of each in each individual. Nilzen employed this method with great satisfaction, using 0.05 cc. of the combined material intradermally. One might also introduce both the histamine and the antihistaminic by iontophoresis if one wants to avoid injection technique.